

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

IN RE: Acetaminophen – ASD-ADHD
Products Liability Litigation

Docket No.: 22-md-3043 (DLC)

This Document Relates To:

All Cases

**DEFENDANTS' REPLY IN SUPPORT OF MOTION TO EXCLUDE PLAINTIFFS'
GENERAL CAUSATION EXPERTS' OPINIONS REGARDING BIOLOGICAL
PLAUSIBILITY/MECHANISM**

TABLE OF CONTENTS

	<u>Page</u>
ARGUMENT	2
I. PLAINTIFFS MISCONSTRUE THE GOVERNING LAW.	2
II. PLAINTIFFS’ EXPERTS DO NOT RELIABLY ANALYZE THE RELEVANT LITERATURE.	4
A. Plaintiffs’ Experts Cherry-Pick From Hundreds Of Findings To Highlight The Few That Arguably Support Their Opinions.	5
B. [REDACTED]	8
III. PLAINTIFFS’ MECHANISTIC THEORIES ALL RELY ON UNRELIABLE LEAPS IN LOGIC.	9
A. Plaintiffs Have Not Identified The Underlying Neurostructural Mechanisms That Cause ASD Or ADHD.	9
B. Each Of Plaintiffs’ Mechanistic Theories Fails For Different Reasons.	12
CONCLUSION	17

TABLE OF AUTHORITIES**Page(s)****CASES**

<i>In re Accutane Products Liability</i> , 511 F. Supp. 2d 1288 (M.D. Fla. 2007)	2
<i>Daniels-Feasel v. Forest Pharmaceuticals, Inc.</i> , No. 17-4188, 2021 WL 4037820 (S.D.N.Y. Sept. 3, 2021)	4, 13
<i>Daubert v. Merrell Dow Pharmaceuticals, Inc.</i> , 43 F.3d 1311 (9th Cir. 1995)	10
<i>In re Fosamax Products Liability Litigation</i> , 645 F. Supp. 2d 164 (S.D.N.Y. 2009)	2, 3, 4
<i>Hendrix v. Evenflo Co.</i> , 255 F.R.D. 568 (N.D. Fla. 2009).....	4
<i>In re Mirena IUD Products Liability Litigation</i> , 169 F. Supp. 3d 396 (S.D.N.Y. 2016)	15
<i>In re Mirena IUD Products Liability Litigation</i> , 202 F. Supp. 3d 304 (S.D.N.Y. 2016)	8
<i>In re Mirena IUS Levonorgestrel-Related Products Liability Litigation</i> , 341 F. Supp. 3d 213 (S.D.N.Y. 2018)	passim
<i>In re Rezulin Products Liability Litigation</i> , 369 F. Supp. 2d 398 (S.D.N.Y. 2005)	7, 8
<i>Siharath v. Sandoz Pharmaceuticals Corp.</i> , 131 F. Supp. 2d 1347 (N.D. Ga. 2001)	8
<i>In re Zolofit (Sertraline Hydrochloride) Products Liability Litigation</i> , 26 F. Supp. 3d 466 (E.D. Pa. 2014)	11

RULES

Fed. R. Evid. 702	5
Prop. Fed. R. Evid. 702.....	15

OTHER AUTHORITIES

Anand, <i>Perinatal Acetaminophen Exposure & Childhood Attention-Deficit/Hyperactivity Disorder (ADHD): Exploring the Role of Umbilical Cord Plasma Metabolites in Oxidative Stress Pathways</i> , 11(10) Brain Sci. 1302 (2021).....	12
Bauer, <i>Consensus Statement: Paracetamol Use During Pregnancy—A Call for Precautionary Action</i> , 17 Nature Revs. Endocrinology 757 (2021).....	3
Bauer, <i>Prenatal Paracetamol Exposure and Child Neurodevelopment: A Review</i> , 101 Horm. Behav. 125 (2018).....	3
Carey, <i>Examining Associations Between Prenatal Biomarkers of Oxidative Stress & ASD-Related Outcomes Using Quantile Regression</i> , 53(8) J. Autism Dev. Disord. 2975 (2023).....	12
Faraone, <i>The World Federation of ADHD International Consensus Statement: 208 Evidence-Based Conclusions About the Disorder</i> , 128 Neurosci. Biobehav. Rev. 789 (2021).....	11
Liu, <i>Oxidative Stress in Autism Spectrum Disorder—Current Progress of Mechanisms and Biomarkers</i> , 13 Frontiers in Psychiatry 1 (2022).....	11
Nasim, <i>Relationship Between Antioxidant Status & Attention Deficit Hyperactivity Disorder Among Children</i> , 10 Int’l. J. Prev. Med. 1 (2019)	12
<i>Reference Manual on Scientific Evidence</i> (3d ed. 2011)	5
Rigobello, <i>Perinatal Exposure to Paracetamol: Dose and Sex-Dependent Effects in Behaviour and Brain’s Oxidative Stress Markers in Progeny</i> , 408 Behav. Brain Res. 1 (2021).....	6, 7
Tyl, <i>Identification & Interpretation of Developmental Neurotoxicity Effects: A Report from the ILSI Research Foundation/Risk Science Institute Expert Working Group on Neurodevelopmental Endpoints</i> , 30 Neurotoxicol. Teratol. 349 (2008)	7

Plaintiffs' oppositions essentially abandon all but two of their experts' speculative and unscientific mechanism theories, focusing their efforts on oxidative stress and vague endocannabinoid alterations. Even as to those theories, their arguments confirm that their experts' theories are untested, unsupported hypotheses, and are thus inadmissible under Rule 702.

First, there is no truth to plaintiffs' claim that defendants improperly seek to hold plaintiffs' experts to a standard of "certainty," rather than plausibility. The law is clear that expert opinions regarding biological plausibility cannot be based on a mere hypothesis or guesswork. Instead, as plaintiffs' own authority recognizes, the experts must have scientific evidence that the mechanism they propose is supported by reliable scientific data. That evidence is manifestly absent here.

Second, plaintiffs' insistence that their experts' approach to animal studies was nominally based on a weight-of-the-evidence methodology, and that this suffices to survive Rule 702 scrutiny, is also wrong. The question under Rule 702 and *Daubert* is whether the experts reliably **applied** a valid methodology. They did not. Instead, they cherry-picked isolated positive results, while disregarding negative results that undermine their opinions in a results-oriented manner. Plaintiffs try to distract the Court from that failing by noting that JJCI's own consultant assessed animal studies. But a manufacturer's assessment of animal data does not constitute an endorsement of its use for purposes of establishing general causation, and in any event, the consultant's consideration—unlike that of plaintiffs' experts—was careful and methodical, not selective and biased, further highlighting the unreliability of plaintiffs' experts' opinions.

Third, plaintiffs fail to refute defendants' arguments regarding the multiple other methodological holes in their experts' opinions. Most fundamentally, plaintiffs do not seriously

dispute that their experts cannot describe the mechanics of either ASD or ADHD, an omission other courts have deemed fatal to biological plausibility opinions. Instead, plaintiffs attempt to shift the burden of proof onto defendants to *disprove* plaintiffs' experts' sweeping claim that oxidative stress and endocannabinoid alterations cause both ASD and ADHD. But defendants have no burden to prove a negative, and this strategy cannot overcome the paucity of scientific support for plaintiffs' experts' theories, which rest on mere hypotheses rather than plausible science.

ARGUMENT

I. PLAINTIFFS MISCONSTRUE THE GOVERNING LAW.

As set forth in defendants' opening brief, Drs. Cabrera, Louie and Pearson do not (and cannot) reliably opine that there is a plausible mechanism by which in utero acetaminophen exposure can cause either ASD or ADHD. Plaintiffs respond that they do not have a burden to "prove[]" biological plausibility to a "certainty" (Pearson Opp'n at 18-19; Louie Opp'n at 13-14; Cabrera Opp'n at 28), but that is not the standard defendants have advanced, and while the bar is lower than certainty, it is higher than plaintiffs' experts can reach. Courts consistently reject biological plausibility theories that are "merely . . . unproven hypothes[e]s" unsupported by "evidence of [how] the mechanism . . . works." *In re Accutane Prods. Liab.*, 511 F. Supp. 2d 1288, 1295 (M.D. Fla. 2007); *accord In re Mirena IUS Levonorgestrel-Related Prods. Liab. Litig.*, 341 F. Supp. 3d 213, 305 (S.D.N.Y. 2018) ("untested mechanism hypothesis" "is not reliable" and "is beset by analytic and evidentiary gaps at multiple steps"), *aff'd*, 982 F.3d 113 (2d Cir. 2020). And "the significance of this factor increases," where, as here, "epidemiological evidence is lacking or inconclusive." *In re Fosamax Prods. Liab. Litig.*, 645 F. Supp. 2d 164, 181 (S.D.N.Y. 2009).

Plaintiffs do not seriously dispute that their experts’ opinions on biological plausibility are just that—i.e., untested “hypothes[es].” (Pearson Opp’n at 19.) Instead, they argue that their experts’ proposed mechanism theories pass muster under *Daubert* because they were also “hypothesized” by a group of scientists who signed the so-called Bauer Consensus Statement. (*Id.*) But that document—which, notably, generated a “consensus counterstatement”—merely urged the “initiation of epidemiological and experimental studies to understand the hormonal, epigenetic and metabolic mechanisms by which APAP acts and might adversely affect development.”¹ Dr. Bauer’s call for more research echoes her earlier paper (relied upon by Dr. Baccarelli), which described the biological theories being pressed in this case as mere “hypotheses.”²

Plaintiffs’ authority is not to the contrary. For example, in *In re Fosamax*, 645 F. Supp. 2d at 170—which is cited heavily throughout plaintiffs’ opposition briefs³—the plaintiffs alleged that bisphosphonates, a bone resorption inhibitor used to treat osteoporosis, caused a rare condition called “osteonecrosis of the jaws (‘ONJ’).” *Id.* The parties agreed on the actual mechanics of ONJ itself—i.e., it is a disease consisting of “an area of dead jaw bone that becomes exposed to the oral cavity.” *Id.* The only dispute concerned *how* bisphosphonates actually cause that dead area of jawbone, which occurred, according to the plaintiffs’ experts, when bisphosphonates accumulated in the jaw bone, resulting in “suppression of bone turnover.” *Id.* at 182. The court held that this opinion was admissible because the proposed theory was “widely reported in the scientific literature as a plausible explanation,” with “[n]early every

¹ Bauer, *Consensus Statement: Paracetamol Use During Pregnancy—A Call for Precautionary Action*, 17 *Nature Revs. Endocrinology* 757, 758-59 (2021) (Mot. Ex. 39).

² Bauer, *Prenatal Paracetamol Exposure and Child Neurodevelopment: A Review*, 101 *Horm. Behav.* 125 (2018) (Mot. Ex. 40).

³ Cited in Louie Opp’n at 14, 18; Pearson Opp’n at 4, 19; Cabrera Opp’n at 17, 19.

report and review of [the condition] point[ing] to bisphosphonate-induced remodeling suppression as a likely mechanism” and even the American Dental Association “conclud[ing] that biologic plausibility point[s] in the direction of causality.” *Id.* (citation omitted).

No comparable evidence exists in this case, which is one reason why the FDA once again rejected a “determination of [a] causal[]” relationship earlier this year.⁴ Unlike ONJ, ASD and ADHD are neurodevelopmental disorders, the mechanics of which are not fully understood by the medical community. Plaintiffs do not even claim that their experts “know[] ‘the precise pathogenesis of’” ASD or ADHD (Pearson Opp’n at 28-39 (citation omitted)), much less that such processes are understood within the broader medical and scientific community. And “until such time as medical science understands the physiological process by which” these complex neurodevelopmental disorders arise and develop, “the law cannot impose liability for” them. *Hendrix v. Evenflo Co.*, 255 F.R.D. 568, 602 (N.D. Fla. 2009) (applying principle to opinion regarding ASD), *aff’d*, 609 F.3d 1183 (11th Cir. 2010). In short, because “[t]he courtroom is not the place for scientific guesswork” (i.e., “[l]aw lags behind science; it does not lead it”), plaintiffs’ experts’ untested hypotheses on biological mechanisms are unreliable. *In re Mirena*, 341 F. Supp. 3d at 270-71 (citation omitted).

II. PLAINTIFFS’ EXPERTS DO NOT RELIABLY ANALYZE THE RELEVANT LITERATURE.

An expert opinion is not reliable merely because the expert identifies, and claims to have followed, a reliable methodology; rather, the expert must also *apply* that methodology in a reliable manner. *Daniels-Feasel v. Forest Pharms., Inc.*, No. 17-4188, 2021 WL 4037820, at *12 (S.D.N.Y. Sept. 3, 2021) (“an unreliable application of purportedly sound scientific

⁴ See ECF 1105, at 1-2 (“FDA Letter”) (quoting Ex. A to FDA Letter (“FDA 2023 Review”), at 3-4); *see also* ECF 483-1 at FDACDER000114 (“It is unlikely that further observational studies will provide more clarity without more mechanistic data.”).

methodology” does not satisfy *Daubert*), *aff’d*, No. 22-146, 2023 WL 4837521 (2d Cir. July 28, 2023); *see also* Fed. R. Evid. 702 (proponent of an expert’s opinion must demonstrate that the “expert has reliably applied the principles and methods to the facts of the case”). Put another way, “[t]he specific techniques by which the weight of the evidence . . . methodology is conducted must themselves be reliable according to the principles articulated in *Daubert*.” *In re Mirena*, 341 F. Supp. 3d at 248 (citation omitted).

Here, plaintiffs’ experts have not reliably applied their stated methodologies. Instead, they cherry-pick isolated findings in studies with largely null results, without offering a scientific basis for ignoring the findings that do not fit their narrative. And plaintiffs’ efforts to analogize their experts’ methods to those of toxicologists retained by JJCI only highlight the differences between accepted methods and their own unscientific approach.

A. Plaintiffs’ Experts Cherry-Pick From Hundreds Of Findings To Highlight The Few That Arguably Support Their Opinions.

As explained in defendants’ opening brief, plaintiffs’ experts rely on animal studies that involved a wide assortment of behavioral and chemical tests and reported multiple outcomes. If even one of those tests showed a positive result, plaintiffs’ experts counted it as supportive, while ignoring negative findings from the same study. This approach is bad science, in part because of the multiplicity rule: if you run enough tests, at least one is likely to report a positive result purely by chance. (Mot. at 17-21.) *See also Reference Manual on Scientific Evidence* (3d ed. 2011), at 256 (“If enough comparisons are made, random error almost guarantees that some will yield ‘significant’ findings, even when there is no real effect.”)

Plaintiffs’ response is baffling. For starters, they acknowledge the principle that running a large number of tests increases the likelihood that some positive results will be spurious. (Pearson Opp’n at 26.) They also recognize that a null finding is indicative of no

neurodevelopmental effect. (*Id.* at 24 (“If a toxicant did not affect neurodevelopment at all, no change would be observed in any direction.”).) Nonetheless, plaintiffs go on to defend their experts’ methods by disregarding all of these same principles. Plaintiffs assert, for example, that Dr. Pearson reliably counts studies showing changes in glutathione levels (“GSH”) as supportive of his theory, regardless of whether the change is positive or negative (even though he theorizes that acetaminophen increases oxidative stress by decreasing GSH levels, not vice versa). To justify this position, plaintiffs speculate (without referencing any scientific literature) that a study that shows an *increase* of GSH levels (which would seem to rebut Dr. Pearson’s theory) means that acetaminophen “might initially cause [GSH levels] to decrease, leading the brain to respond by synthesizing more.” (Pearson Opp’n at 23.) Null findings likewise pose no problem for Dr. Pearson’s opinions because, according to plaintiffs, “[a]bsence of evidence is not the same as evidence of absence.” (*Id.* at 26.) In short, if a single finding shows an adverse effect, it supports Dr. Pearson; if it shows the opposite of an adverse effect, it also supports Dr. Pearson; and if it shows no effect, it does not matter, because at least a few findings showed some kind of change and thus support Dr. Pearson. Under this win-win approach, almost anything ever studied would be a plausible biological mechanism. Plaintiffs’ inability to cite any scientific or legal authority for such an undisciplined method is not surprising.

Plaintiffs’ defense of their experts’ cherry-picking is doubly problematic because they attempt to support their experts’ opinions with justifications the experts themselves do not adopt. A good example is Rigobello 2021, which ran 16 tests on whether acetaminophen decreased levels of GSH and returned *15* results that were null or “showed, if anything, that GSH levels were higher than in the controls.”⁵ (Mot. at 23-24.) In an effort to justify their experts’ focus on

⁵ Rigobello, *Perinatal Exposure to Paracetamol: Dose & Sex-Dependent Effects in Behaviour & Brain’s*

the one favorable result in the study, plaintiffs blame the negative results on low sample size, again without any scientific support or citation. (Louie Opp’n at 17 n.21.) Plaintiffs also attempt to brush away the fact that the single favorable GSH result disappeared at a higher dose (350 mg/kg) by repeating their claim that “higher levels of glutathione present at higher APAP doses could . . . reflect the body’s homeostatic response to the increased toxicant.” (Pearson Opp’n at 36; *see also id.* at 23.) But plaintiffs’ experts have never suggested such an explanation, which the Rigobello 2021 authors described as a “speculative hypothesis.”⁶ Because “[t]he subject of [defendants’] motion is the proposed testimony of experts, not the theories of the lawyers,” *In re Rezulin Prods. Liab. Litig.*, 369 F. Supp. 2d 398, 407 (S.D.N.Y. 2005), plaintiffs’ attempts to backfill their opinions with missing explanations would fail even if they were not speculative.⁷

Defendants similarly highlighted the fact that Dr. Louie ignored the findings of Klein 2020, a study that plaintiffs’ other experts relied on for its behavioral findings but discounted for its mechanistic findings—namely, that “acetaminophen exposure in utero had no significant effect on GSH levels . . . after birth.” (Mot. at 22-23.) According to plaintiffs, Dr. Louie did so “because the relevant information from that study was contained in and cited by Rigobello (2021), which he did review.” (Louie Opp’n at 17.) But plaintiffs cite no testimony or statement in either of Dr. Louie’s reports purporting to offer such an explanation. And Dr. Louie could not have been aware that Klein 2020 and Rigobello 2021 contained the same information because he

Oxidative Stress Markers in Progeny, 408 Behav. Brain Res. 1 (2021) (“Rigobello 2021”) (Mot. Ex. 122).

⁶ *Id.* at 5.

⁷ Plaintiffs’ interpretation of Rigobello 2021 also flies in the face of the Tyl 2008 article on which they heavily rely, which states that “a modest difference from control that is statistically significant **but inconsistent with a pattern of effect** (i.e., does not occur in a dose-related manner and is not accompanied by any other DNT or toxic effects) may be considered an incidental finding that is unrelated to treatment.” Tyl, *Identification & Interpretation of Developmental Neurotoxicity Effects: A Report from the ILSI Research Foundation/Risk Science Institute Expert Working Group on Neurodevelopmental Endpoints*, 30 Neurotoxicol. Teratol. 349, 377 (2008) (emphasis added) (Opp’n Ex. 131).

admitted that he had “*never read*” Klein 2020 before it was shown to him at his deposition. (Dep. of Stan Louie (“Louie Dep.”) 259:10-15 (emphasis added) (Mot. Ex. 10).) For this reason, too, plaintiffs’ arguments fail.

B. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] *See In re Mirena IUD Prods. Liab. Litig.*, 202 F. Supp. 3d 304, 324-25 (S.D.N.Y. 2016) (“These emails ‘demonstrate that [Bayer] employees raised questions’ about the timing of perforations in Mirena users They do not amount to admissions that secondary perforation exists.”) (citation omitted); *accord Siharath v. Sandoz Pharms. Corp.*, 131 F. Supp. 2d 1347, 1367-69 (N.D. Ga. 2001) (animal studies conducted by the defendant did not constitute a reliable basis for a theory of general causation), *aff’d sub nom. Rider v. Sandoz Pharms. Corp.*, 295 F.3d 1194 (11th Cir. 2002).

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] Plaintiffs’ experts, by contrast, did not take account of this bigger picture presented in Blecharz-Klin 2017. Instead, they narrowly focused only on the results

favorable to their opinions without considering the broader context of other findings in the study. (*See, e.g.*, Am. Rep. of Robert Cabrera at 100-01 (Mot. Ex. 6) (crediting simply the “reported changes in the amino acid levels in the hippocampus and cortex”); Am. Rep. of Brandon Pearson (“Pearson Rep.”) at 89-90 (Mot. Ex. 8) (not recognizing that more than a third of the observed neurochemical responses did not follow a monotonic dose-response).)

Plaintiffs’ experts’ analyses also contradict each other, further revealing the non-scientific nature of their approach. Plaintiffs assert, for example, that Dr. Pearson was right to ignore that Blecharz-Klin 2014 reported no effect on “certain amino acids in the hippocampus” because the study “involved APAP treatment on *adult* rats” and, thus, is “not relevant to whether *prenatal* APAP exposure contributes to ASD or ADHD.” (Pearson Opp’n at 22-23.) But in another brief, plaintiffs argue that defendants are wrong to criticize Dr. Cabrera for relying on adult rodent studies because “adult-rodent studies can show a given mechanism at work.” (Cabrera Opp’n at 26.) Similarly, plaintiffs attempt to turn Dr. Pearson’s outcome-oriented selection of studies that form the basis of his opinions into a virtue by arguing that only those studies met “his criteria for data relevance” (Pearson Opp’n at 13 n.4), but in so arguing, they undermine Dr. Cabrera’s consideration of studies that Dr. Pearson explicitly deemed not relevant—such as studies involving adult rodents (*see* ASD Br. at 65 (ECF 1160)).

Plaintiffs’ inability to defend their own experts without arguing against themselves further highlights the arbitrary and unscientific nature of these experts’ analyses.

III. PLAINTIFFS’ MECHANISTIC THEORIES ALL RELY ON UNRELIABLE LEAPS IN LOGIC.

A. Plaintiffs Have Not Identified The Underlying Neurostructural Mechanisms That Cause ASD Or ADHD.

As defendants’ opening brief emphasized, courts have repeatedly recognized that a plausible mechanistic theory must begin with an understanding of how the injury in question

generally develops. (See Mot. at 12-14 (citing *Mirena* and *Hendrix*).) Plaintiffs respond by arguing that Dr. Louie was not “entirely ‘silen[t]’ on ‘the basic operation of the “mechanism” and “pathway”” allegedly linking acetaminophen to ASD and ADHD (Louie Opp’n at 15), but this argument addresses the wrong problem. In order to offer a reliable biological plausibility opinion, an expert must understand the mechanisms by which the injury generally develops. Plaintiffs’ experts do not. Plaintiffs also assert that “scientific understanding of ASD and ADHD and their causal factors has improved considerably since *Hendrix*” (Louie Opp’n at 15), but they offer no explanation of how it has improved or what supportive information is known now about the pathophysiology of these conditions that was not known in 2009.

Plaintiffs’ principal case, *In re Fosamax* (cited in Louie Opp’n at 14, 18; Pearson Opp’n at 4, 19; Cabrera Opp’n at 17, 19), illustrates precisely what is lacking in this litigation. As mentioned above, there, the actual *mechanics* of the disorder were not in dispute; the only question was how the drug at issue could cause the disease. Plaintiffs also cite the Ninth Circuit’s decision on remand in *Daubert*, which stated that “[c]ausation can be proved even when we don’t know precisely how the damage occurred, if there is sufficiently compelling proof that the agent must have caused the damage somehow.” (Pearson Opp’n at 29-30 (quoting *Daubert v. Merrell Dow Pharms., Inc.*, 43 F.3d 1311, 1314 (9th Cir. 1995)).) The Ninth Circuit went on to give the example of “50 people who [ate] at a restaurant one evening” and “c[a]me down with food poisoning during the night,” *Daubert*, 43 F.3d at 1314, but that sort of overwhelming circumstantial evidence is lacking here. To the contrary, the epidemiologic evidence is weak and confounded, as defendants have explained in great detail. (See ASD Br. at 27-47; ASD Reply at 6-27, incorporated herein; ADHD Br. at 18-37 (ECF 1162); ADHD Reply at 2-17, incorporated herein).)

Plaintiffs also contend that Dr. Pearson offered “[g]raphical depiction[s] of the ways oxidative stress can perturb neurodevelopment and lead to neurodevelopmental disorders.” (Pearson Opp’n at 30 (citation omitted).) But a series of summary graphics with the words “Neurodevelopmental disorder,” “Neuro-inflammation,” “Cerebral injury” and “Neuro-dysfunction” and arrows pointing to “ASD” does not describe the “mechanics” underlying the complex disorders at issue. *In re Mirena*, 341 F. Supp. 3d at 248. At best, they illustrate a hypothesis. Moreover, the graphic plaintiffs pasted into their brief is excerpted from an article that describes it as “depicting the ***potential*** mechanisms of oxidative stress in the pathogenesis of ASD.”⁸

Plaintiffs’ experts’ conflation of ASD and ADHD further highlights their inability to explain the underlying mechanism of either disorder. (*See* Mot. at 16-17.) Plaintiffs’ briefs parrot their experts’ assertions that “there is scientific consensus that ASD and ADHD have a shared pathophysiology, overlapping biological pathways, and shared causal factors.” (Louie Opp’n at 16.) The only article plaintiffs cite for support, however, merely states that certain studies have shown that ADHD shares certain “genetic and environmental influences” with “many other psychiatric disorders (e.g. schizophrenia, depression, bipolar disorder, autism spectrum disorder, conduct disorder, eating disorders, and substance use disorders) and with somatic disorders (e.g. migraine and obesity),” and that such findings “***suggest*** that these disorders also share a pathophysiology in the biological pathways.”⁹ That “suggest[ion]” does not suffice. *See In re Zolof (Sertraline Hydrochloride) Prods. Liab. Litig.*, 26 F. Supp. 3d 466,

⁸ Liu, *Oxidative Stress in Autism Spectrum Disorder—Current Progress of Mechanisms and Biomarkers*, 13 *Frontiers in Psychiatry* 1, 3-4 (2022) (emphasis added). Copies of all studies cited herein and not previously provided are attached to the Declaration of Kristen L. Richer as Exs. 2-14.

⁹ Faraone, *The World Federation of ADHD International Consensus Statement: 208 Evidence-Based Conclusions About the Disorder*, 128 *Neurosci. Biobehav. Rev.* 789, 795 (2021) (emphasis added) (Opp’n Ex. 93).

474 (E.D. Pa. 2014) (“To meet the *Daubert* standard, the experts must demonstrate that these opinions are based on methods and procedures of science, not speculation.”).

B. Each Of Plaintiffs’ Mechanistic Theories Fails For Different Reasons.

Plaintiffs’ experts’ mechanism opinions are unreliable for other reasons too, none of which are rebutted in their opposition briefs.

First, plaintiffs ignore the bulk of defendants’ arguments regarding the literature surrounding their oxidative stress theory. (*See* Mot. at 21-28.) As defendants explained in their opening brief, a major deficiency surrounding that theory is plaintiffs’ experts’ failure to actually link oxidative stress to either ASD or ADHD. Plaintiffs are unable to refute this argument. (*See* Mot. at 27-28.) Plaintiffs point to Nasim 2019,¹⁰ which measured antioxidant levels in children with ADHD (Louie Opp’n at 16), but they do not address the cautionary statement in Carey 2023 that “retrospective studies in children already diagnosed with ASD cannot provide evidence as to whether [oxidative stress] differences are a cause *or a consequence* of ASD.”¹¹ The same logic holds true of ADHD as well. Plaintiffs also cite Anand 2021¹² as supportive of their experts’ opinions, but they seem to have missed the authors’ cautionary statement: “Given the observational study design, this study should be interpreted as *hypothesis generating and not causal*.”¹³

¹⁰ Nasim, *Relationship Between Antioxidant Status & Attention Deficit Hyperactivity Disorder Among Children*, 10 Int’l. J. Prev. Med. 1 (2019) (Opp’n Ex. 160).

¹¹ Carey, *Examining Associations Between Prenatal Biomarkers of Oxidative Stress & ASD-Related Outcomes Using Quantile Regression*, 53(8) J. Autism Dev. Disord. 2975, 2976 (2023) (emphasis added) (Mot. Ex. 54).

¹² Anand, *Perinatal Acetaminophen Exposure & Childhood Attention-Deficit/Hyperactivity Disorder (ADHD): Exploring the Role of Umbilical Cord Plasma Metabolites in Oxidative Stress Pathways*, 11(10) Brain Sci. 1302 (2021) (Opp’n Ex. 142).

¹³ *Id.* at 12 (emphasis added).

Plaintiffs' cursory treatment of Adverse Outcome Pathway ("AOP") 20, relied on heavily by Dr. Cabrera, also highlights the problem. (*See* Cabrera Opp'n at 29-30.) As explained in defendants' opening brief, although this AOP purports to link proteins that can bind to thiol (SH)- and seleno-containing proteins involved in protection against oxidative stress (a group that includes GSH) to impairment in "learning and memory," the AOP does not reference ADHD at all, and all references to autism were excised by the authors following criticisms from reviewers. (*See* Mot. at 27-28.) Specifically, one of the peer reviewers from the EPA noted that "autism is described by a set of very serious social behavior problems which may or may not involve [learning and memory] problems," and a reviewer from the Canadian government questioned whether the "AOP [is] related to ASD," requesting that the autism references be removed if not. (Opp'n Ex. 200, at 7, 13.) Plaintiffs' and Dr. Cabrera's rejection of the authors' and reviewers' own conclusion that AOP 20 does not relate to ASD highlights the unreliability of Dr. Cabrera's opinions. *See, e.g., Daniels-Feasel*, 2021 WL 4037820, at *4, *10 (noting that an expert "must not exceed the limitations the authors themselves place on [a] study" and excluding expert because he "press[ed] conclusions that the . . . authors were not willing to make") (citation omitted).

Plaintiffs also fail to rehabilitate their experts' reliance on many studies that did not involve brains—much less fetal brains—without showing that effects on other organs would be similar to those in the brain. (*See* Mot. at 25-26.) This is problematic, as defendants explained in their opening brief, because different organs have unique structures and contain different concentrations of chemicals and enzymes. (*Id.*) For example, plaintiffs provide no evidence that NAPQI has ever been detected in the fetal brain. CYP2E1—the enzyme key in forming NAPQI—is barely present in the fetal brain but abundant in the liver, meaning that extrapolating

from studies examining oxidative stress in the liver is not necessarily informative as to what happens to the fetal brain. (*Id.*) While plaintiffs acknowledge the different levels of CYP2E1 briefly in a footnote and claim that it does not matter because there is at least some “presence” of CYP2E1 in the fetal brain (Pearson Opp’n at 37 n.13), they ignore that Dr. Louie conceded that the levels of CYP2E1 are ***much*** lower in the brain than in the liver, but did not consider that difference in forming his opinions (*see* Mot. at 26; *see also* Louie Dep. 193:14-194:8). In fact, the brain also has higher levels of GSH than the liver, meaning that it can more quickly detoxify any NAPQI, further highlighting the unreliability of focusing on liver studies to learn about the brain. (*See* Mot. at 26.)

In short, plaintiffs’ experts’ oxidative stress theory rests on faulty scientific principles and should be rejected.

Second, plaintiffs’ experts’ theory that acetaminophen somehow interferes with the endocannabinoid system, which then causes ASD and ADHD, amounts to nothing more than rank speculation. Once again, plaintiffs fail to tie any changes in the endocannabinoid system to either ASD or ADHD. *See In re Mirena*, 341 F. Supp. 3d at 285 (giving “scant attention to the actual pharmacokinetic process that must underlie the causal sequence that he postulates” is a “failure[] of methodology” warranting expert’s exclusion). In fact, nowhere in their briefs do plaintiffs even identify the ways endocannabinoid disruptions allegedly cause ASD or ADHD, relying instead on studies that have “linked [endocannabinoid disruption] to ASD” or “support an association with ADHD.” (Pearson Opp’n at 8.) As explained in defendants’ opening brief, these studies serve, at best, to link a “biomarker” alteration “with ASD or ADHD” without explaining which is the chicken and which is the egg. (Mot. at 30-31.) Plaintiffs try to flip the *Daubert* burden by complaining that defendants did not “cite . . . scientific support for their

speculation that changes to the endocannabinoid system are somehow ‘just as likely to result from ASD or ADHD as to cause it’” (Pearson Opp’n at 39 (citation omitted)), but (again) the burden is on *plaintiffs* to show that endocannabinoid system changes are a cause of either disorder. As defendants have repeatedly explained, they do not have to prove the negative: to disprove a causal pathway that plaintiffs have not even established. *See* Prop. Fed. R. Evid. 702; *see also In re Mirena IUD Prods. Liab. Litig.*, 169 F. Supp. 3d 396, 418-19 (S.D.N.Y. 2016) (rejecting the “general thrust of [p]laintiffs’ arguments,” to the effect that defense experts did not “point[] to studies ruling out the possibility of secondary perforation”).

In any event, plaintiffs do not even attempt to defend the myriad missing links in the other parts of the causal chain of the endocannabinoid theory. As defendants previously explained, plaintiffs’ experts lack “evidence that acetaminophen prevents reuptake or increases free levels of endocannabinoids” and rely on “nothing but speculation and strained analogy to support the hypothesis that endocannabinoid dysregulation in utero causes ASD or ADHD.” (Mot. at 29.) Plaintiffs offer no meaningful response. Nor do they explain how their experts can extrapolate from studies like Schultz 2012, which found that soaking mouse neurons in an acetaminophen metabolite solution (but not an acetaminophen solution) induced cell death similar to an anandamide solution, to conclude that acetaminophen causes ASD or ADHD. (*Id.*) Even if plaintiffs could connect any changes to the endocannabinoid system with ASD or ADHD, these missing links would render their hypothesized causal chain speculative and inadmissible. *See In re Mirena*, 341 F. Supp. 3d at 270-71 (excluding theory of biological plausibility that “relie[d] on too many unsupported leaps”).

Third, plaintiffs have all but abandoned each of their other proposed biological pathways. As for epigenetics, plaintiffs hardly mention the topic despite the pages defendants devoted to the

proposed pathway in their opening brief (*see* Mot. at 31-34), and they explicitly concede that Dr. Louie “does not intend to testify that DNA methylation is a plausible mechanism for acetaminophen elevating the risk of ASD and ADHD” (Louie Opp’n at 18-19). The most attention plaintiffs pay to epigenetics comes in a footnote in their brief defending Dr. Pearson, and even then, plaintiffs fail to meaningfully address the flaws in his opinion. Plaintiffs respond that Dr. Pearson “considered the relevant studies, including on DNA methylation” and “his report has a section on epigenetic changes” (Pearson Opp’n at 38 n.14), but the most that section of Dr. Pearson’s report establishes is that “epigenetic disruptions can also perturb normal cellular processes, and contribute to the development of toxicological outcomes, including diseases and adverse effects on health”—not ASD or ADHD specifically. (Pearson Rep. at 60-61.) Plaintiffs offer no other defense of that speculative and broad purported mechanism for harm.

Plaintiffs similarly throw in the towel on their other hypotheses related to levels of non-endocannabinoid neurotransmitters, BDNF levels, cell death, and prostaglandin disruption (*see* Mot. at 35-39), half-heartedly defending all of these mechanisms in a single paragraph in which they afford each mechanism no more than two sentences (*see* Pearson Opp’n at 39). In that brief space, plaintiffs do not address their experts’ failure to harmonize the BDNF findings in Viberg 2014 and Klein 2020 (*see* Mot. at 35-36), do not explain how cell death would be connected to a clinically relevant outcome of ASD or ADHD (*see id.* at 37-38), and do not elaborate on why any link between prostaglandin disruption and ASD or ADHD is more than rank speculation when other analgesics also disrupt prostaglandin but have never been suggested to increase the risk of ASD or ADHD (*see id.* at 38-39). Plaintiffs’ cursory treatment of those mechanisms is consonant with the speculative nature of the evidence “supporting” those pathways. Indeed, Dr. Cabrera himself conceded at his deposition that “outside of the endocannabinoid and the

oxidative stress” pathways, there “would be gaps in the data that would leave a gap in the biological plausibility that would need additional data to fill in those gaps.” (Dep. of Robert Cabrera 325:2-326:1 (Mot. Ex. 7).) For this reason, too, the experts’ opinions should be excluded.

CONCLUSION

For the foregoing reasons, the Court should exclude all of plaintiffs’ experts’ opinions on proposed biological mechanisms.

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Respectfully submitted,

By: /s/ Kristen L. Richer

Kristen L. Richer

BARNES & THORNBURG LLP

2029 Century Park East, Suite 300

Los Angeles, CA 90067

Tel (310) 284-3896

Fax (310) 284-3894

Kristen.Richer@btlaw.com

*Defense Liaison and Member of the Retailer
Liaison Committee*

Sarah E. Johnston (admitted *pro hac vice*)

BARNES & THORNBURG LLP

2029 Century Park East, Suite 300

Los Angeles, CA 90067

Tel (310) 284-3880

Fax (310) 284-3894

Sarah.Johnston@btlaw.com

Manufacturer Liaison

Jessica Davidson (admitted *pro hac vice*)

SKADDEN, ARPS, SLATE, MEAGHER
& FLOM LLP

One Manhattan West

New York, New York 10001

Tel (212) 735-3000

Fax (212) 735-2000

Jessica.Davidson@skadden.com

On the Brief

Kristen R. Fournier
KING & SPALDING LLP
1185 Avenue of the Americas, 34th Floor
New York, NY 10036
Tel (212) 556-2100
Fax (212) 556-2222
KFournier@kslaw.com
Member of the Retailer Liaison Committee

Lori B. Leskin
ARNOLD & PORTER KAYE SCHOLER LLP
250 W. 55th Street
New York, NY 10019
Tel (212) 836 8000
Fax (212) 836 8689
Lori.Leskin@arnoldporter.com
Member of the Retailer Liaison Committee